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Microbiological Study Findings and Their Clinical Predictors In Culture-Diagnosed Septic Knee Arthritis Patients In The Somali Population

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ABSTRACT

Septic arthritis (SA) is a serious orthopedic emergency. Waiting for aspiration and microbiological analysis results may cause therapeutic delay, resulting worsening of prognosis. In this study, it was aimed to determine the predictive value of clinical signs, laboratory and radiological examinations for the diagnosis of culture-proven SA and SA agents, and to create projections for early treatment.

This 7-year retrospective cohort study included adult patients with suspected SA seen in a tertiary hospital emergency department. Patients with a positive culture aspiration confirming septic arthritis at one joint were analyzed, and then compared to a control group defined as 'Aseptic Arthritis' (ASA).

While Acute onset (P=0.038), history of crystal-induced arthritis (P=0.022) were significantly higher in the aseptic arthritis group, the presence of pain increasing with movement (P=0.042), previous septic arthritis history (P=0.028), higher than 0.5 ng/mL serum procalcitonin value (P=0.048), purulent appearance of synovial fluid (P=0.028) were found to be significantly higher in the septic arthritis group. However, septic arthritis patients significantly had a synovial fluid WBC count of over 20,000/µL and a PMNs ratio of over 75%. Pain that increases with movement Methicillin-resistant S. aureus was highly effective in differentiating (P=0.048).

Although the definition of SA or its diagnostic criteria have not yet been determined, a few factors we found in our study results, the cutoff values we suggested, and the definition of "Aseptic Arthritis" that we used in our study design may be thought-provoking in terms of determining the diagnostic criteria for SA.

Keywords: Septic Arthritis, emergency department, microbiological analysis, predictors

Introduction

Septic arthritis (SA) is still a common and serious orthopedic emergency. While the overall incidence of SA is 2-10 per 100,000, this rate rises to 30-70 in patients with joint replacement (1). 27% of the patients who applied to the emergency department with the complaint of joint swelling were diagnosed with septic arthritis (2). The reason for this high rate is that these patients mostly apply to the emergency department, and in chaotic emergency room conditions, it is very unlikely that an emergency physician will aspirate or wait for the results of microbiological analysis. On the other hand, with any therapeutic delay, prognosis worsens and SA can cause loss of joint function, sepsis and mortality rates of 11% (3). On the other hand, other inflammatory arthropathies may show similar clinical findings and usually do not require surgical intervention. For these reasons, the clinician must be able to differentiate between these to prevent undertreatment of septic arthritis or overtreatment of other inflammatory arthropathies. In this context, the physician needs strong clinical, laboratory and radiological predictors for diagnosis and early initiation of treatment.

Diagnostic criteria for septic arthritis are still undetermined. A positive fluid culture taken from the joint is usually used for diagnosis, and this may take some time to result (4). Direct gram staining to be performed until the culture results are available is positive only in 25% to 50% of the cases (5). In addition, studies on the sensitivity of clinical findings, serum laboratory tests, radiological findings, and initial synovial fluid findings in patients presenting with suspected SA have mixed results, and data on the specificity of these predictors are very limited (5-7). For these reasons, it is often difficult to determine the probability of making a decision to initiate

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hospitalization, medical or surgical treatment in a patient with suspected SA.

This is a retrospective study aiming to determine the predictive value of clinical signs, laboratory and radiological examinations for the diagnosis of culture-proven septic arthritis. In this study, the clinical features and diagnostic behaviors of the causative microorganisms were also examined and thus, it was aimed to create projections for empirical treatment.

Materials and Methods

Data collection and processing: This 7-year retrospective cohort study was conducted at the Recep Tayyip Erdoğan Training and Research Hospital, the only tertiary care hospital in central Mogadishu, between July 2014 and July 2021 with institutional ethics committee approval (approval number MSTH-8134). Electronic medical records of all patients were obtained from the "Hospital Information Management System" and analyzed comprehensively. According to the International Classification of Diseases (ICD) 10, patients presenting with septic arthritis clinical findings were identified, and the preliminary diagnosis and definitive diagnosis were recorded. Patient demographics, time of onset of symptoms (acute<24 hours), presence of fever (>38°C), local findings, pain at rest and on movement, risk factors, treatments received prior to admission were recorded. Radiological findings suggestive of SA (decreased joint space, radiological findings of subchondral joint destruction) and the presence of existing arthropathy were recorded from radiology reports or evaluated by a radiologist if not present. If done, joint ultrasound results were noted.

Additional data included rough appearance results (clear, turbid, purulent or hemorrhagic) of joint fluid classified and reported by the microbiologist, cytology, presence of microcrystals, gram stain and culture analysis results. When the clinical sample is evaluated with gram stain in our microbiology laboratory, 20-40 areas containing cells and bacteria are scanned and the white blood cell is investigated as the host cell. If no microorganism or cell is seen, it is reported as 'No microorganism seen' or 'No cell found'. In order to ensure a higher rate of reproduction in cultures, the liquid is sent to the laboratory without delay and with the test request form attached. Agar plates and blood media are also inoculated on Ziehl Neelsen media in order not to miss the diagnosis of tuberculosis due to the high prevalence of tuberculosis in Somalia. Taking into account the sample type, bacteria that represent typical morphologies are indicated in the report. Empirical treatment was antibiotics initiated before a causative pathogen was identified. Definitive or adjusted therapy was antibiotics administered or prescribed according to the pathogen isolated in the culture positive group. In order to determine the etiology of SA and extra-articular infection focus, the patients were evaluated for hematogenous and contiguous spread.

Inclusion and exclusion criteria: Patients with joint prosthesis, joint trauma, open fracture, intra-articular surgery (arthroplasty surgery, intra-articular steroid injection, etc.), patients receiving antibiotics before aspiration, patients with immunodeficiency (transplant patients receiving anti-rejection drugs, cancer receiving chemotherapy or patients with inflammatory disorders receiving immune system therapy are defined as patients receiving modulating drugs) and patients who did not applied aspiration and were not hospitalized, were excluded from the study. Apart from these, patients who were hospitalized due to clinical findings suggestive of SA, whose serum/synovial fluid laboratory and culture analyzes and radiological examinations were performed, were included in the study.

Definitions: Hematogenous spread (sinusitis, bronchiectasis, endocarditis, meningitis or other) was defined as a blood culture positivity, spread from the adjacent infected focus (inoculation) as the presence of an infection site that may be a source of infection (osteomyelitis, insect bites, clinical finding and newly proven radiological findings suggesting adjacent joint, skin or bone infection). Leukocytosis was defined as a serum white blood cell (WBC) count >15,000/mm3. Increased erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum procalcitonin (PCT) were respectively defined as any value exceeding 20 mm/hr or value above 5 mg/dL and value above 0.5 ng/mL. Physical examination findings suggestive of SA was defined as one or more symptoms with pain that increases with movement or pain that increases with movement, laboratory findings suggestive of SA was defined as the presence of serum WBC count >15,000/mm3 and/or CRP > 5 mg/dL, radiological findings suggestive of SA was defined as the presence of at least one of the radiological findings suggestive of septic arthritis.

Patients with a positive culture aspiration confirming SA in the affected joint were defined as "Acute Septic Arthritis". Then, patients with

negative culture aspiration were analyzed. Those who did not receive antibiotics before aspiration, were evaluated as negative in terms of spread from the extra-articular infection focus (hematogenous spread, inoculation), and whose prediagnosis (septic arthritis) was changed by the orthopedist, that is, the diagnosis was not protected by antibiotic treatment for at least 14 days by the clinician, and culture-negative patients who were not treated accordingly were defined as "Acute Aseptic Arthritis". Then these two groups (Septic Arthritis-Aseptic Arthritis) were compared.

Statistical Analysis: Descriptive univariate statistics were used for data analysis; for continuous variables were presented as mean±standard deviation, and categorical variables for absolute numbers and proportions (%). The chi-square test and cross-tabulations were used to compare variables between SA and ASA patients. P-value < 0.05 was considered significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS -IBM) for Windows version 25.

Results

Demographics and clinical data: During the study time, 1,174 patients were admitted to the emergency department due to complaints and symptoms suggestive of SA. After the initial evaluation, arthrocentesis was performed in 486 patients who were evaluated as possible SA. Among these, 394 patients met our inclusion criteria and formed our study population. In our study population, 253 patients (64.2%) were culture positive. The demographic characteristics of these patients and their distribution according to predictive definitions (clinical, laboratory, radiological) are summarized in Table 1. In order to determine the etiology of SA and the extra-articular infection focus, the patients were evaluated for hematogenous and contiguous spread. The rate of blood culture positivity, defined as hematogenous spread, was 47.8% (n=121) in the SA group. As a result of our evaluation for inoculation, 72 patients (28.5%) in the SA group had radiological evidence for a contiguous focus of infection: fifteen confirmed by initial or subsequent follow-up plain radiographs, thirty-three confirmed by both MRI and plain radiographs, and twenty-four confirmed by computed tomography (CT).

Laboratory and radiologic findings: Those with a procalcitonin value of 0.5 ng/mL and above were significantly more common in the SA group (10.6% vs 34.4%, P=0.048). When the applied joint ultrasound (n=276, 70.1%) analysis results were evaluated, no difference was found between the SA and ASA groups in terms of the presence of effusion (P=0.073).

Synovial laboratory test values: The synovial fluid WBC count under 20,000 was significantly more common in the ASA group, while the synovial fluid WBC count was significantly more common in the SA group, above 20,000 (Table 2). The rate of synovial fluid PMNs in the ASA group was significantly more common below 75, while the rate of synovial fluid PMNs (%) in the SA group was significantly more common than 75 and above.

Microbiology: Table 3 contains the revealing analysis of septic arthritis predictors (clinical, laboratory, radiological, microbiological findings) identified and classified for diagnostic purposes by the causative microorganisms detected in the culture. Classification of causative microorganisms was designed to guide empirical treatment. Thus, it was aimed to determine the diagnostic behavior of causative microorganisms and to obtain statistically significant data that could guide empirical treatment (early treatment) without waiting for culture results. S. aureus remains the most common isolate in patients with septic arthritis and was the most frequently isolated bacteria in our study (67.2%). Physical examination findings suggestive of SA were present in the entire Methicillin-resistant S. aureus group and this was statistically significant compared to other bacterial groups (100%, P=0.048). However, the rate of synovial fluid >90% PMN suggestive of SA was significantly lower in Mycobacteria than in the others (22.7%, P=0.038). Mycobacterium tuberculosis (68.4%) was the most frequently isolated agent in septic arthritis cases due to mycobacterial infection in Somalia, and Mycobacterium avium complex was found to be the most common agent in non-tuberculous mycobacterial (NTM).

Treatment and outcomes: In our study, intravenous treatment was applied to 372 patients and oral treatment was applied to only 17 patients. The coverage rate for in the SA group of empirical intravenous therapy (n=308) was 71.1% (90.8% in the ASA group). While methicillin-resistant S. aureus coverage rate of empirical treatment was 21.6%, mycobacteria coverage rate was only 9.4%. In the SA group, the number of patients who did not receive definitive or corrected treatment after empirical treatment (the empirical treatment was not changed) was 98 (54.4%). A total of 187

Table 1. Distribution of patients by demographic characteristics and predictive definitions

	Total (n=394)	Septic arthritis (n=253)	Aseptic arthritis (n=141)	P- value
Age, Mean ± SD	47.8±17.6	46.7±11.4	51.3±21.2	0.067
Gender, male	260 (%66.0)	165 (%65.2)	95 (%67.4)	0.054
Symptoms duration				
Acute onset, <24h	187(%47.5)	79(%31.2)	108(%76.6)	0.038
Risk factors				
History of septic arthritis	93(%23.6)	82(%32.4)	11(%7.8)	0.028
Diabetes Mellitus	79(%20.1)	53(%20.9)	26(%18.5)	0.815
History of crystal-induced arthritis	55(%13.9)	16(%6.3)	39(%27.7)	0.022
History of rheumatic disease	66(%16.8)	49(%19.4)	17(%12.1)	0.075
Selected Clinical findings				
Fever (t°≥ 38°C)	151(%38.3)	102(%40.3)	49(%34.8)	0.714
Swelling	364(%92.4)	235(%92.9)	129(%91.5)	0.836
Redness	137(%34.8)	91(%35.1)	46(%32.6)	0.612
Heat	290(%73.6)	192(%75.9)	98(%69.5)	0.584
Pain that increases with movement	229(%58.1)	187(%73.9)	42(%29.8)	0.042
Serum Laboratory findings				
Serum WBC count >15.000/mm3	203(%51.5)	136(%53.8)	67(%47.5)	0.082
ESR > 20 mm/h	356(%90.3)	240(%94.9)	116(%82.3)	0.067
CRP > 5 mg/dL	279(%70.8)	196(%77.5)	83(%58.9)	0.072
PCT ≥ 0.5 ng/mL	102(%25.9)	87(%34.4)	15(%10.6)	0.048
Radiological findings suggestive of SA *	154(%39.1)	103(%40.7)	51(%36.2)	0.092

* Presence of one or more of the following symptoms: decrease in joint space width, subchondral demineralization, erosive joint destruction

patients (47.5%) underwent arthroscopic drainage. Arthroscopic drainage decision was made mostly (62.9%) without culture results and according to the characteristics of the aspiration fluid (purulent or cloudy appearance, WBC count/μL≥50,000, PMNs ratio≥90%). The rate of surgical intervention (performed before culture results are available) for in the SA group was higher, although not significantly, compared to the ASA group, but included only half of the patients (50.9% vs. 41.1%, p=0.846). In-hospital mortality rate was higher in the SA patients than in the ASA patients (12.3% vs. 2.1%, P=0.045).

Discussion

In our study, physical examination findings (presence of increased pain with movement), time of symptom onset (acute onset), risk factors (crystal-induced arthritis and previous history of septic arthritis), serum laboratory values (Procalcitonin ≥ 0.5 ng/mL), and synovial fluid analysis results (purulent appearance, WBC>20,000/μL, PMNs ratio>75%) were the parameters that best predictors of SA. In addition, pain that increases with movement predicted Methicillin-resistant S. aureus, and synovial fluid >90% PMNs ratio predicted Mycobacteria bacillus. In our evaluation in terms of treatment, we found that while the coverage rate of methicillin-resistant S. aureus and mycobacteria was low, empirical antibiotherapy was applied to almost all of the ASA patients and surgery was performed in a significant proportion of ASA patients.

During the study period, 21.6% of our patient cohort with suspected SA was confirmed. In our evaluation in terms of septic arthritis etiology and

Table 2. Diagnostic Value of Synovial Fluid Characteristics

	Total (n=394)	Septic arthritis (n=253)	Aseptic arthritis (n=141)	P- value
Gross appearance				
Clear	48(%12.2)	0(%0)	48(%34.1)	<0.001
Turbid	145(%36.8)	79(%31.2)	66(%46.8)	0.062
Purulent	152(%38.6)	140(%55.3)	12(%8.5)	0.028
Hemorrhagic	49(%12.4)	34(%13.5)	15(%10.6)	0.087
WBC count/ µL				
< 100	0	0	0	
100-1.999	26(%6.6)	5(%1.9)	21(%14.9)	0.023
2.000-19.999	124(%31.5)	41(%16.2)	83(%58.9)	0.034
20.000-49.999	123(%31.2)	99(%39.2)	24(%17.1)	0.050
50.000-99.999	92(%23.4)	79(%31.2)	13(%9.1)	0.047
≥100.000	29(%7.3)	29(%11.5)	0	<0.001
PMNs ratio (%)				
<25	26(%6.6)	9(%3.6)	17(%12.0)	0.052
25-49	63(%16.1)	24(%9.5)	39(%27.8)	0.042
50-74	85(%21.5)	29(%11.4)	56(%39.7)	0.048
75-89	114(%28.9)	106(%41.9)	8(%5.6)	0.020
≥90	106(%26.9)	85(%33.6)	21(%14.9)	0.050
Presence of microcrystals	142(%36.1)	79(%31.2)	63(%44.7)	0.098
Positive Direct Gram Stain	107(%27.2)	98(%38.7)	9(%6.4)	0.034

infection spread, we found the most common hematogenous spread. While the rate of hematogenous spread in SA patients was 47.8% (n=121), the inoculation rate was 28.5%. This result emphasizes the importance of holistic evaluation in the management of probable or confirmed cases of septic arthritis in terms of investigating the mode of spread and focus of infection and initiating early treatment of other related foci simultaneously. This result can also be explained by the lack of adequate organization and infrastructure for primary health care, antibiotic supply in Somalia. The risk factors for SA (>80 years of age, diabetes, rheumatoid arthritis) have a comparable incidence in both groups (8). Unlike, the data of our study obtained results that are not compatible with the literature. In terms of risk factors for SA, while history of septic arthritis was more common in the SA cases (P=0.028), diabetes and rheumatoid arthritis did not show a statistically significant difference. In our study, among the physical examination findings suggestive of SA, pain that increases with movement was the parameter that best distinguished SA from cases without SA. A previous study found that joint pain and swelling had a high predictive value, but laboratory tests were more reliable than examination findings (5). Likewise, Acute onset (<24h) in terms of symptoms duration was predictive for SA patients. In our study, serum WBC count >15,000/mm3, ESR >20 mm/hr, and CRP >2 mg/dL had a low predictive value for SA. Our study results, in line with the literature, have shown that regardless of the threshold level used for these parameters (WBC, ESR, and CRP), it does not increase the possibility of being the posttest for SA (5, 9-11). In a previous study, a threshold value of 0.4 ng/dl was found to be specific and sensitive to detect SA (7). In our study, those with a procalcitonin value of 0.5 ng/mL and above were found to be significantly more common in the SA group (P=0.048), and this result supported the cut-off value found in the literature in terms of procalcitonin predictiveness. In our study results, radiological findings were low predictive of SA (P= 0.092). Although the definition of radiological findings poses a challenge, previous studies have reported that these findings are seen in approximately 50% of patients with SA (12).

Table 3. Diagnostic Behavior of Causative Microorganisms

	Total n=253	Gram positive bacteria n=183	Methicillin-resistant S. aureus n=116	Gram negative bacteria n=31	Anaerobes n=17	Mycobacteria n=22	P-Value
Physical examination findings suggestive of SA*	187(%73.9)	144(%78.7)	116(%100)	21(%67.7)	10(%58.8)	12(%54.5)	0.048
Laboratory findings suggestive of SA†	196(%77.5)	151(%82.5)	102(%87.9)	19(%61.3)	12(%70.6)	14(%63.6)	0.092
Radiological findings suggestive of SA ‡	103(%40.7)	69(%37.7)	52(%44.8)	14(%45.2)	9(%52.9)	11(%50.0)	0.117
Purulent appearance of synovial fluid	140(%55.3)	102(%55.7)	48(%41.4)	18(%58.1)	8(%47.1)	12(%54.5)	0.086
Synovial WBC count ≥20.000/ µL	207(%81.8)	157(%85.8)	110(%94.8)	23(%74.2)	14(%82.3)	13(%59.1)	0.654
PMNs ≥75%	191(%75.5)	146(%79.8)	101(%87.1)	25(%80.7)	15(%88.2)	5(%22.7)	0.038

* One or more symptoms with pain that increases with movement or pain that increases with movement
† Presence of serum WBC count >15,000/mm3 and/or CRP > 2 mg/dL
‡ Presence of at least one of the radiological findings suggestive of septic arthritis

Evaluation and interpretation of synovial fluid appearance is often subjective and difficult to standardize. In our study, the gross appearance of the synovial fluid was a valid parameter in excluding SA when the fluid was clear or predicting SA when it was purulent (P=0.028), and this result was consistent with the literature (13). Studies evaluating the diagnostic power of articular fluid findings for the diagnosis of SA have found conflicting results. For example, a previous study found that synovial cell count and polymorphonuclear cell percentage were the most powerful tests predicting SA (5). While a synovial cell count of 25,000 to 50,000 cells/µL has an odds ratio of 2.9 for septic arthritis, a cell count odds ratio of >50,000 cells/µL is 7.7. A synovial fluid cell count of 50,000 cells/µL or higher is typically associated with septic arthritis in a natural joint, while lower values are more consistent with a crystalline or inflammatory arthropathy (14-18). However, the literature supporting this cutoff is quite limited, but this value is treated dogmatically. On the other hand, Li et al reported that the number of 50,000 cells had only 50% sensitivity and instead of this, they recommended a threshold value of 17,500 to maximize sensitivity (83%) and specificity (67%). That is, they suggested using this limit to help rule out septic arthritis rather than diagnose it (15). Our study results led us to recommend using the cutoff values we found (WBC>20,000/µL and PMNs ratio>75%) to help rule out septic arthritis rather than diagnose it. In our study results, we found that 31.2% of the patients with SA had microcrystals. In this respect, our results were consistent with the literature reporting a similar frequency (21%), and the presence of microcrystals did not exclude SA (19).

In this study, unlike other studies, the diagnostic trends and predictors of bacteria that cause septic arthritis and their effects on guiding empirical treatment, on which there is still no consensus, were also examined. Pain that increases with movement predicted Methicillin-resistant S. aureus

and was highly effective in differentiating from other bacteria (sensitivity 100, P=0.048). It should be noted that during our study period, 22 patients with septic arthritis caused by confirmed mycobacterial infection were identified. In culture-negative SA cases with specific risk factors and unresponsive to standard empirical therapy, mycobacterial infection should be considered. In addition, mycobacterial bone infection should be definitely considered in patients presenting with findings of insidious onset and relatively localized bone infection, and biopsy specimens should be obtained when suspected in these patients. In our study data, synovial fluid >90% PMNs ratio was found to be significantly lower in the group with Mycobacteria bacillus isolated (P=0.038) and it was again decisive. In this sense, our result is remarkable in terms of mycobacterial infections, which are not usually considered in the differential diagnosis and can cause severe complications if not treated early.

Regarding treatment, long-term parenteral antibiotic therapy was administered to SA cases in our population. Our mean duration of antibiotic therapy was 39 days, of which 23 days included intravenous therapy. While empirical intravenous therapy had a high coverage rate for SA patients overall, it had low coverage for MRSA and mycobacteria. In addition, about half of the empirical therapy started had to be changed. We found that surgical intervention (before the culture results are available) was applied to only half of the SA patients, on the other hand, a significant amount of unnecessary surgical procedures were performed in ASA patients. These results represented the inability of our empirical treatment to cover the causative microorganism and unnecessary overtreatment, that is, treatment failure. Before empiric and specific antibiotic therapy was started, the SA mortality rate was approximately 60% (20-22). Today, although it varies with the presence of accompanying comorbidities (renal and cardiac insufficiency, immunosuppression, age), the mortality rate of SA is between 10-20% (10,23,24). In our study, the in-hospital mortality rate was 12.3%, and it was consistent with the literature.

Limitations: The difficulty in the methodology is the classification of Septic and Aseptic arthritis. In this study, a comparison was made between the group that included only culture-proven septic arthritis cases (to limit the inclusion of false-positive patients) (to exclude false positive patients) and the control group (aseptic arthritis), in which culture-negative SA cases were tried to be excluded as much as possible. In this way, we may have missed some cases of septic arthritis, and the prevalence of this condition has been reported between %7-35 in previous studies (2,25,26). However, our aim was not to determine the incidence of septic arthritis in our study population, but to identify clinical predictors for initiating early treatment in patients with true septic arthritis without waiting for microbiology results. There is no gold standard for the diagnosis of septic arthritis, except that the general judgment of an experienced clinician has been demonstrated to be superior to any laboratory or radiological examination (27,28). Therefore, we included the clinician's judgment in the identification criteria we set for the control group. Still, this may not serve as a perfect comparison group. However, these pragmatic definitions have attempted to obtain the most accurate comparison group, and their data are useful for comparison with patients with culture-positive septic arthritis.

No clinical finding or non-bacteriological test alone has a definitive predictor for the diagnosis of SA. The diagnosis of septic arthritis is the peak of the clinician's experience, together with the patient's clinical, laboratory and radiological findings. Therefore, the definition of SA or the diagnostic criteria have can not yet been determined. However, apart from our findings supporting the results of previous studies, a few factors we found in the results of the study, the cutoff values we suggested and the definition of "Aseptic Arthritis" that we used in our study design may be thought-provoking in terms of determining the diagnostic criteria for SA. In this context, it is important to emphasize that despite our strict definitional criteria for septic and aseptic arthritis, our sample size was higher than previous studies and the value of the results and statistical analyzes obtained accordingly increased. In addition, it is possible that the analysis method we designed to detect the causative bacteria and the results we obtained may provide projections for further microbiological analysis.

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